HYPERTENSION
pharmacological treatment
Etiopathogenesis of essential hypertension (EH)

Cause of EH is abnormality of blood pressure regulation at different levels:

1) CNS cortex regulation
2) Sympathoadrenal system
3) Renin - angiotensin – aldosterone
4) Renal - tubular system
5) vasodilatation system (kinins, natriuret. hormons, prostanoids, EDRF/NO,...)
Important and probably decisive bases for regulatory systems abnormalities are their genetic polymorphism
Possibility of hypertension treatment according genotype (polymorph. with accent to RAA)
## Classification (WHO/ISH, JNC VI)

<table>
<thead>
<tr>
<th></th>
<th>syst. BP</th>
<th>diast. BP</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>NORMOTENSION</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>optimal BP</td>
<td>&lt;120</td>
<td>&lt;80 mm Hg</td>
</tr>
<tr>
<td>normal TK</td>
<td>&lt;130</td>
<td>&lt;85 mm Hg</td>
</tr>
<tr>
<td>higher normal BP</td>
<td>130-139</td>
<td>85-89 mm Hg</td>
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<tr>
<td><strong>HYPERTENSION</strong></td>
<td></td>
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<tr>
<td>gr. 1 (mild)</td>
<td>140-159</td>
<td>90-99 mm Hg</td>
</tr>
<tr>
<td>gr. 2 (medium)</td>
<td>160-179</td>
<td>100-109 mm Hg</td>
</tr>
<tr>
<td>gr. 3 (severe)</td>
<td>≥180</td>
<td>≥110 mm Hg</td>
</tr>
</tbody>
</table>
BP target level after treatment:

• **old patients:**
  target normotension (TK <140/90)

• **adults, diabetics, renal or heart failure:**
  normal BP (<130/85 mmHg) or
  „optimal“ BP (<120/80 mm Hg)
Cardiovascular risk for patients with hypertension in relation to other risk factors
Decrease of CV risk for general population (HOT study)

optimal diastolic and systolic BP
Morbidity and control of hypertension in ČR 2000/10

- Screened: 3325
  - Normotension: 2084 (62.7%)
    - Not diagnosed: 414 (20.4%)
    - Not treated: 202 (19.3%)
    - Unsatisfactory controlled: 385
  - Hypertension: 1241 (37.3%)
    - Diagnosed: 827 (66.6%)
      - Treated: 625 (50.4%)
      - Well controlled: 240 (19.3%)
Hypertension is badly controlled all over the world (also in Czech Republic)

More tough criteria for control hypertension

Necessary to increase detection and treatment!

Combination therapy offers better control
Main pharmacotherapeutic classes:

- diuretics
- β-blockers
- calcium channels blockers (CCB)
- ACE inhibitors
- angiotensin II receptor blockers (AT$_1$)
- α- blockers - periphery
- centrally acting drugs:
  - α$_2$-receptors agonists
  - imidazoline receptors agonists
- direct vasodilators
DIURETICS FOR TREATMENT HYPERTENSION
DIURETICS – main classes

- loop diuretics
- distal tubulus (thiazides)
- potassium sparing diuretics
- aldosterone receptor blockers
- aquaretics (vaptans)
Effect of diuretics

- Osmotic diuretics, methylxanthines
- Carboanhydrase inhibitors
- Osmotic diuretics

Amilorid, triamteren

Thiazides, indapamid

Loop diuretics

Aldosterone receptors

Na\(^+\), H\(_2\)O

H\(_2\)O
DIURETICS
mechanism of actions

- Decreased plasma and tissue level of sodium – vasodilatation,
- Better plasticity of vessel wall
- Decreased volume of intravascular fluid – decrease of BP
DIURETICS

- equivalent to other antihypertensive drugs – high cost-effectiveness

- optimal antihypertensive for old patients with systolic hypertension

- thiazides first choice (combination with amiloride), event. diuretics with vasodilatation properties (indapamide),

- furosemide not used
DIURETICS

- low doses preferred
- with respect to activation of RAA combination with β-blockers, ACEI or sartans is feasible
- risk of hypokalemia (especially for older patients)
TUBULAR DIURETICS - THIAZIDES

Na⁺/Cl⁻ co-transport inhibition at distal part

- low diuretic effect,
- slow onset of action, long half-life, stable bioavailability
- not useful for patients with severe renal impairment,
- first choice antihypertensives
DISTAL TUBULUS DIURETICS - THIAZIDES

- **hydrochlorothiazid**  (6-12 h, 6,25 mg),
- **chlorthalidion**  (48-72h, 6,25-25 mg)
  - 1x daily or every second day
  - chlorthalidion longer effect

- **indapamid**: also vasodilatation
  (16-36 h, 2,5 mg)
DISTAL TUBULUS DIURETICS - THIAZIDES

ADVERSE EVENTS

- **Hypokalaemia**  Increase Na-K exchange
- hyponatremia, hypovolemia, hypotension

Metabolic effect – higher doses:
- glycid and lipid metabolic impairment, hyperurikemia

Prevention

- Low doses
- Carefully for diabetics
KALIUM SPARING DIURETICS

- Na⁺ channel inhibition – distal part

- **amiloride**: small diuretic effect, slow onset of action, long half-live (days), suitable for combination with other diuretics, also for IHD

- **triamteren**: less favourable, short diuretic effect

- combination with loop diuretics has better patients prognosis

- Side effects: hyperkalemia
Diuretics should be a part of any combination therapy of hypertension, they are safe, effective and cheap.
PHARMACOLOGY of \( \beta \)-BLOCKERS AND CLINICAL USE
<table>
<thead>
<tr>
<th></th>
<th>α a β-adrenergic stimulation effect</th>
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<tbody>
<tr>
<td>α1</td>
<td>smooth muscle (vasc., GU)</td>
</tr>
<tr>
<td></td>
<td>liver</td>
</tr>
<tr>
<td></td>
<td>heart</td>
</tr>
<tr>
<td></td>
<td>contraction</td>
</tr>
<tr>
<td></td>
<td>glykogenolysis</td>
</tr>
<tr>
<td></td>
<td>↑ contractility</td>
</tr>
<tr>
<td>α2</td>
<td>pankreas (β-bb.)</td>
</tr>
<tr>
<td></td>
<td>smooth muscle (vasc.)</td>
</tr>
<tr>
<td></td>
<td>↓ insulin secretion</td>
</tr>
<tr>
<td></td>
<td>contraction</td>
</tr>
<tr>
<td>β1</td>
<td>myocard</td>
</tr>
<tr>
<td></td>
<td>juxtaglom. apparatus</td>
</tr>
<tr>
<td></td>
<td>↑ HR + conduct., ↑ contractility</td>
</tr>
<tr>
<td></td>
<td>↑ renin</td>
</tr>
<tr>
<td>β2</td>
<td>smooth muscle (vasc., bronch., GU)</td>
</tr>
<tr>
<td></td>
<td>liver</td>
</tr>
<tr>
<td></td>
<td>glyconeogenesis, glycogenolysis</td>
</tr>
<tr>
<td>β3</td>
<td>fat tissue</td>
</tr>
<tr>
<td></td>
<td>lipolysis</td>
</tr>
</tbody>
</table>
β-BLOCKERS
- mechanism of action

- heart rate and output
- effect in CNS
- renin release
- myocardial stabilization (↓ fibril. threshold)
- apoptosis (remodeling)
- response to stress
CARDIOSELECTIVITY
- $\beta_1 + \beta_2$ receptor block

a) cardioselective
- Effect mainly limited to myocardial receptors $\beta$
- *atenolol, betaxolol, bisoprolol, metoprolol*,

b) non-selective
- Block of extracardial receptors $\beta_2$ (event. $\beta_3$)
  (broncho- and vasoconstriction, $\downarrow$ lipolysis and insulin secretion)
- *metipranol, pindolol, bopindolol*
The impact of CARDIOSELECTIVITY

- higher impact on ↓ mortality + morbidity secondary prevention in HF treatment

- ↓ incidence of adverse metabolic events

- better tolerance (vaso-, bronchoconstriction)
Comparison of selectivity index in essential cardioselective β-blockers
ISA PRESENCE

- the effect on $\beta$-receptor stimulation
  - (partial agonism)

$\beta$-block. with ISA: *pindolol, bopindolol*...

$\beta$-block. without ISA: *atenolol, betaxolol, bisoprolol, metoprolol, metipranol*....

importance of ISA – not important

- reduced bradycardia ??
- ↓ therapeutic effect in secondary prevention
Inverse relation between the heart rate and life length
HYDROPHILIC x LIPOPHILIC

a) lipophilic molecules
   - easy penetration into CNS (insomnia, depression)
   - metabolised in liver (↓ bioavailability)
   - variable blood level (CYP polymorphism)
     - metoprolol, ...

b) hydrophilic molecules
   - ↓ incidence of adverse events (centrally conditioned)
   - excreted in kidney (longer effect, ↑ availability)
     - atenolol, bisoprolol ...

No differences in clinical effect
β- BLOCKERS ANTAGONISING α RECEPTORS as well

- α + β receptor blockers:
  - mild vasodilatation
  - ↓ negative metabolic impact
  - reduced bronchoconstriction

- significant effect in HF treatment

- carvedilol, bisoprolol, (labetalol)
Comparison of biological half-life of essential cardioselective β-blockers

- Acebutolol: 7-13
- Atenolol: 6-9
- Betaxolol: 14-20
- Bisoprolol: 12-17
- Celiprolol: 5
- Metoprolol: 3-4
- cardioselective
- without ISA, medium lipophilic
- Long halflife (15-20 h)
- vasodilatation by block of calcium channel
- preferable dose/effect ratio
BISOPROLOL

- high cardioselectivity, without ISA, hydrophilic
- long halflife (10-11 h);
- effect in CHF
METOPROLOL

- medium cardioselective, significant lipophilic without ISA,
- shorter half-life (3 h)
- polymorph metabolism
- low-dose presentation
- ↑ effect in hypertension
ATENOLOL

medium cardioselectivity, hydrophilic, without ISA,
- medium lasting effect (t1/2 6-9 h)
- low incidence of „central“ adverse events
NEBIVOLOL

- **medium cardioselectivity**, hydrophilic without ISA
- biological halflife 8-27 h.
  (polymorphism in metabolism)
- Significant vasodilatation nitrate like effect
CELIPROLOL

- high cardioselectivity
- hydrophilic with ISA
- longer biological halflife (6-8 h)
- vasodilatation
  (mediated via $\beta_2$ receptor stimulation)
ESMOLOL

- high cardioselectivity, without ISA
- very short half-life (minutes)
- parenteral application in acute state

ACEBUTOLOL

- medium cardioselectivity, hydrophilic
- with low ISA
- long biological half-life (8-12 h)
CARVEDILOL

- relative cardioselectivity
  medium biol. halflife (6-8 h)
  - significant vasodilatation

- $\alpha$-lytic effect
  - most effective drug in HF
CARDIOVASCULAR INDICATIONS β-BLOCKERS

- Hypertension
- Ischemic heart disease:
  - AMI
  - MI – secondary prevention
  - AP, silent ischemia
- Heart failure
- Arrhythmias
β-blockers - contraindications

nonselective
• conductivity disturb.
• signif. bradycardia
• feochromocytoma
• asthma,
• ischemia lower extremities,
• depression
• diabetes
• dyslipidemia

selective
• conductivity disturb.
• signif. bradycardia
• feochromocytoma
• asthma,
• bronchospasm.
β-BLOCKERS in patients with BRONCHIAL OBSTRUCTION

- COPD and asthma - β-blockers contraindication (20%)
- Retrospect. analysis 115 000 patients after MI:
  40% asthma and COPD patients well tolerated
  β-blockers, significantly reduced mortality by 14% (J. Chen, 2001)

- Asthma is no longer seen as absolute contraindication in highly β₁-selective blockers (e.g. bisoprolol, betaxolol)
\textbf{\(\beta\)-BLOCKERS INDICATION IN HYPERTENSION}

- accompanying IHD
- younger patient with hyperkinetic circulation
- pregnancy (cardioselective BB)
- in elderly, including isolated systolic hypertension
- hypertensive patient with heart failure (carvedilol, metoprolol, bisoprolol)
- Drug of choice in monotherapy or combination
ANTIHYPERTENSION DRUGS SUITABLE FOR COMBINATION with $\beta$-BLOCKERS

- diuretics
- CCB dihydropyridine type
  - (verapamil, diltiazem causing bradycardia – attention)
- ACE inhibitors and sartanes
- $\alpha$-blockers
- vasodilators and centrally acting drugs
β- BLOCKERS ANTAGONISING α RECEPTORS as well

- blockade receptor α:
  - mild vasodilatation
  - ↓ negative metabol. impact
  - reduced bronchoconstriction

- significant effect in HF treatment
  - karvediol, bisoprolol, (labetalol)
ACE INHIBITORS and SARTANES in HYPERTENSION
Renin-angiotensin systém inhibition

ANGIOTENSININOGEN

AT I

AT II

rec. AT₁

RENIN inhib. renine, β-block.

ACE inhib. ACE, inhib. vasopept.

AT₁ blockers (sartans)
ACE INHIBITORS
MECHANISM of ACTION

1) AI to AII conversion inhibition
2) Slow down degradation of bradykinin and neurokinins
ACE INHIBITORS

PHARMACODYNAMIC EFFECT

- ↓ peripheral resistance - VASODILATATION
- ↓ aldosterone and ADH release + ↓ thirst
- ↓ SODIUM and WATER RETENTION
- ↓ NOREPINEHRINE RELEASE
- specific dilatation of vas efferens

NEPHROPROTECTION

- fibrinolysis stimulation (↑ t-PA/PAI-1)
- antimitogenic activity + apoptosis inhibition
- endothelial dysfunction adjustment
Comparison of biological halflife

- **kapto-**
- **quina-**
- **enala-**
- **fosino-**
- **imida-**
- **lisino-**
- **moexi-**
- **perindo-**
- **cilaza-**
- **rami-**
- **spira-**
- **trandola-**

Halflife ACE-I

- **1x daily**
- **2x daily**

zdroj: platná SPC
<table>
<thead>
<tr>
<th>ACE Inhibitor</th>
<th>Dose</th>
</tr>
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<tbody>
<tr>
<td>Enalapril</td>
<td>2x 5-20 mg</td>
</tr>
<tr>
<td>Fosinopril</td>
<td>1x 10-20 mg</td>
</tr>
<tr>
<td>Imidapril</td>
<td>1x 5-10 mg</td>
</tr>
<tr>
<td>Lisinopril</td>
<td>1x 20-80 mg</td>
</tr>
<tr>
<td>Moexipril</td>
<td>1x 7,5-15 mg</td>
</tr>
<tr>
<td><strong>Perindopril</strong></td>
<td>1x 4-8 mg</td>
</tr>
<tr>
<td>Quinapril</td>
<td>1-2x 5-20 mg</td>
</tr>
<tr>
<td>Ramipril</td>
<td>1x 2,5-10 mg</td>
</tr>
<tr>
<td>Spirapril</td>
<td>1x 6 mg</td>
</tr>
<tr>
<td><strong>Trandolapril</strong></td>
<td>1x 2-4 mg</td>
</tr>
</tbody>
</table>
Contraindications ACE-I

- gravidity 2. + 3. trimester
- kidney malformation

- Hyperkalemia
- Aortal stenosis
- cardiomyopathy
ACE-I adverse events

- **cough** (20-30%) decreased dose or stop treatment
- **hyperkalemia** (mainly in combination with sartans)
- **angioedém** (0,1%)
- **hypotension**, first dose effect
- **renal failure - impairment** (decreased filtration pressure)
ACEI indications

- Arterial hypertension
- Chronic heart failure
- Stabilisation of nephropatic progression (mainly diabetic)
- Better prognosis and decreased mortality for ICHS and stroke
ACEI advantages in hypertension

- No metabolic effects,
  (no influence on glucose and lipid metabolism)
- Most effective inhibition of heart hypertrophy
- Regression of myocardial fibrosis
Sartans
(AT$_1$ receptor inhibitors)
ANGIOTENSIN II ANTAGONISTS (RECEPTOR AT1) - SARTANS

- AII acts on AT1 and AT2 receptors
- **RECEPTORS AT1**: responsible for the AII effect (aldosterone secretion, vasoconstriction, sodium retention)
- **RECEPTORS AT2**: may be just mitogenic effect

- AT1 antagonists do not ↑ bradykinin level
- antihypertension effect is ↓ compared to ACE inhibitors - better tolerance (cough)
AT1 receptor blockers effects

- vasodilatation, ↓ perif. resistance (effect smaller than in ACE inhibitors)
- ↓ water retention
-LV morphological change are inhibited
  (↓ apoptosis, necrosis)
- ↓ sympathetic activity
- specific vas efferens dilatation
  (↓ intraglomerular pressure)
- endothelial dysfunction improvement ???
Available sartans

- **losartan** – first generation, short half-life, 
  (2x daily)

- **kardesartan** – long half-life
- **irbesartan** – comparable effects
- **telmisartan** – no special differences
- **valsartan**
SARTANS plasmatic halflife

Plasma halflife (h)

- Eprosartan
- Losartan
- Valsartan
- Candesartan
- Olmesartan
- Irbesartan
- Telmisartan

Range
SARTANS
receptor binding power

Receptor dissociation half life (min)

Valsartan  Losartan\(^{\dagger}\)  Candesartan  Olmesartan  Telmisartan

\(^{\dagger}\) Active metabolite EXP3174
SARTANS indications

- Arterial hypertension
- Stabilisation of nephropatic progression (mainly diabetic)
- Decreased risk of atrial fibrillation
- Beter prognosis and decreased mortality for IHD and stroke
- Chronic heart failure
SARTANS

adverse events and contraindications

**AE**: same as ACEI, much less cough

- best tolerated antihypertensives
- hypotension, (with hypovolemia)
- renal function impairment
  (decreased filtration pressure)
- hyperkalémia
- angioedem (rare)

**Contraindications**:

- **gravidity** (from 2. trimester)!!
- Bilateral renal kidney stenosis
SARTANS - advantages

SARTANS
- Best tolerated antihypertensives
- (50% of AE in comparison to ACE-I)
- Better compliance
- Only telmisartan effective in secondary prevention

ACE-I
- Better effect on mortality for IHD and stroke
- Much better effect for chronic heart failure
- ACE-I more effective for other indications
ALDOSTERONE RECEPTOR INHIBITORS
ALDOSTERONE RECEPTOR INHIBITORS

- aldosterone
- spironolakton
- eplereron
Aldosterone receptors

- kidney - distal tubule
- mineralocorticoid effect (Na\(^+\)/K\(^+\))
- myocard
  - stimulation of fibroblast proliferation
- Vessels smooth muscles and endothel
  - stimulation of fibroblast proliferation
SPIRONOLACTONE

• **myocardial:** fibroblast proliferation inhibition

• **kidney:** distal tubule Na/K pump inhibition, kalium retention and natriuresis (high doses)

• Active metabolite with longer halflife (>15 hod)

• **block of degradation**
  andro-, estro- and gestagens
  (gynaekomastia, menstrual disorders)

• **Risk of hyperkalemia**
EPLERENON

• Similar effect on myocardium and kidney as spironolactone
• **NO block of degradation** andro-, estro- and gestagens
• Better tolerability
• better pharmacoeconomy
CALCIUM CHANNEL BLOCKERS (CCB) in HYPERTENSION THERAPY
CCB – MECHANISM of ACTION in HYPERTENSION THERAPY

- vasodilatation effect
- endothelial dysfunction adjustment
- antiplatelet effect
CALCIUM CHANNEL BLOCKERS (CCB)

- **antihypertensive effect**
  (arteriolar relaxation)

- **antiischemic effect**
  (coronary arteries relaxation et stenotic region)

- **antiarrythmic effect**
  (decreased excitability, conductivity and production of impulses)
CCB

1. generation: abandoned nifedipin, suitable verapamil or diltiazem in retard presentation

2. generation: higher vessel selectivity, shorter halflife, quicker onset of action

3. generation: lipophilic, slower effect onset, long lasting effect
CCB PLASMA HALFLIFE comparison

<table>
<thead>
<tr>
<th>Drug</th>
<th>Halflife $t_{1/2}$ (h)</th>
</tr>
</thead>
<tbody>
<tr>
<td>amlodipin</td>
<td>35-50</td>
</tr>
<tr>
<td>lacidipin</td>
<td>7-16</td>
</tr>
<tr>
<td>isradipin SR</td>
<td>9</td>
</tr>
<tr>
<td>nitrendipin</td>
<td>15-20</td>
</tr>
<tr>
<td>nilvadipin</td>
<td>6-19</td>
</tr>
<tr>
<td>nicardipin</td>
<td>1-4</td>
</tr>
<tr>
<td>nisoldipin</td>
<td>3-6</td>
</tr>
<tr>
<td>nifedipin SR</td>
<td>5-12</td>
</tr>
<tr>
<td>verapamil SR</td>
<td>20-25</td>
</tr>
<tr>
<td>felodipin SR</td>
<td>4-9</td>
</tr>
<tr>
<td>diltiazem SR</td>
<td>5-12</td>
</tr>
</tbody>
</table>
CCB COMPARISON of TIME NEEDED to reach MAXIMAL PLASMA LEVEL

<table>
<thead>
<tr>
<th>Drug</th>
<th>Effect on Set t_{\text{max}} (h)</th>
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<tbody>
<tr>
<td>amlodipin</td>
<td>6-12</td>
</tr>
<tr>
<td>lacidipin</td>
<td>6-12</td>
</tr>
<tr>
<td>isradipin SR</td>
<td>1-2</td>
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<tr>
<td>nitrendipin</td>
<td>1-2</td>
</tr>
<tr>
<td>nilvadipin</td>
<td>1-2</td>
</tr>
<tr>
<td>nicardipin</td>
<td>1-2</td>
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<tr>
<td>nisoldipin</td>
<td>1-2</td>
</tr>
<tr>
<td>nifedipin SR</td>
<td>0.2-0.6</td>
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<tr>
<td>verapamil SR</td>
<td>1-2</td>
</tr>
<tr>
<td>felodipin SR</td>
<td>2-4</td>
</tr>
<tr>
<td>diltiazem SR</td>
<td>1-2</td>
</tr>
</tbody>
</table>

Effect onset t_{\text{max}} (h)
ADVANTAGE OF SLOW ONSET OF THE EFFECT

- slow and stable decrease of BP does not activate regulatory mechanisms

- ADVATAGES OF MINIMAL STIMULATION OF OTHER SYSTEMS (sympatoadrenal and RAA):
  1) antihypertension response is not limited (via vasoconstriction and water retention)
  2) proarhythmic and tachycardia is not involved
  3) metabolic effect is not involved (in intracellular increase of calcium with apoptosis activation, hyperlipidemic + hyperglycemic effect)
RENIN INHIBITORS

- Block of conversion angiotensinogen to ATI (enzyme)
- Block (pro)renin receptors
- Similar effect to ACE-I or sartans
When inhibits RAAS?

- hypertension
- secondary prevention IHD, stroke,
- prophylaxis of left ventricular remodeling and heart failure
- prophylaxis of diabetic nephropathy
ANTIHYPERTENSIVES

2. CHOICE

(EFFECT ON MORTALITY AND MORBIDITY
NOT PROVED)
ANTIHYERTENSIVES

2. CHOICE

• peripheral $\alpha$- blockers

• centrally active drugs:

  alfa$_2$-receptor agonists

  imidazoline receptor agonists

• direct vasodilators
\(\alpha\)-ADRENERGIC RECEPTOR BLOCKERS

- **doxazosin, prazosin**: \(\alpha_1\)-blockers  
  \(\downarrow\) BP + benign prostatic hypertrophy BPH

- **moxonidin, rilmenidin**: arteriolar \(\alpha\)-blockers  
  + central imidazoline \(I_1\) receptor stimulation  
  \(\downarrow\) sympathicus

- **urapidil**: peripheral \(\alpha_1\)-block (vasodilatation)  
  + CNS serotonin receptor block
CENTRALLY ACTING DRUGS

\(\alpha\)-methyldopa:

- pro-drug - \(\alpha\) -methylnoradrenaline
- stimulates presynaptic inhibitory receptors - \(\alpha_2\) in CNS

- Preferably in combinations

- Gravidity
WHY combinations

How to combine
Why combinations?

1) Failure of different regulatory systems plays decisive role in etiopathogenesis of essential hypertension

2) Only with combination therapy was possible to achieve target BP for sufficient proportion of patients populace

3) Combination therapy with different mechanism of action allowed dose decrease and frequency of side effects
Racional and irracional combinations

1) Combination of drugs with different mode of action:

- β-block. + diuretics, CCB, ACE-I, sartanes
- diuretics + β-block., ACE-I, sartanes, CCB
- CCB + β-block., diuretics, ACE-I, sartanes
- ACE-I, sartanes + diuretics, CCB, β-block.

- do not combine ACE-I with sartanes
Racional and irracional combinations

2) combination with potentiation
   - ACE-I + diuretics
   - ACE-I + CCB (in nephropathy)

3) combination leading to ↓ adverse effects
   - β-block. + CCB (vasoconstriction)
   - diuretics + potassium-sparing diuretics (K depletion)
   - diuretics + ACE-I, sartanes (activation RAA)
   - CCB + diuretics (water retention, edema)
Antihypertension drugs combination in associated diseases

- **IHD:** β-blockers + CCB + ACE-I
- **HF:** α,β-blockers + ACE-I + diuretics
- **DIABETES:** β-blockers + sartanes or ACE-I, CCB
- **ID lower extremities:** ACE-I, sartanes, CCB, not β-blockers
- **NEPHROPATHY:** sartanes or ACE-I, CCB
- **PREGNANCY:** methyldopa, β-blockers, hydralazin, Not ACE-I !!!
The main goal of the therapy is to decrease BP. The choice of the antihypertension drug should be made according to associated diseases, potential adverse effects and pharmacoeconomic aspects.